REMARKS/ARGUMENTS

Reconsideration of the application in view of the above amendments and following remarks is requested. Claims 1-6, 9, 11-13, 15, and 17-25 are now in the case. Claims 1, 11, and 17 have been amended. In addition, the specification has been amended at page 3 to correct the reference to the sheets of Fig. 1. No new matter has been added.

Claims 1-6, 9, 11-13, 15, and 17-25 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting. The Office believes that the provisionally rejected claims are unpatentable over claims 41, 42, and 46-54 of copending Application No. 10/139,583.

A Terminal Disclaimer is enclosed herewith. The Terminal Disclaimer is believed to overcome the rejection. This Terminal Disclaimer is filed solely for its statutory function of removing the rejection of double patenting and is not to be regarded as an acquiescence in the merits of the rejection. *Quad Environmental Technologies Corp. v. Union Sanitary District*, 946 F.2d 870, 874, 20 USPQ2d 1392, 1394-95 (Fed. Cir. 1991).

Claims 11-13, 15, 24, and 25 stand rejected under 35 U.S.C. § 112, first paragraph. The Office believes that the claims are not enabled for treating fibrosis caused by zvegf3 "to the extent that treating encompasses completely eliminating and preventing any future occurrence."

This rejection is believed to be overcome by the amendment of claim 11 to recite a method of "reducing" fibrosis. Claims 12-13, 15, 24, and 25 include this limitation in view of their dependence on amended claim 11. This amendment has been made solely to expedite prosecution of claims drawn to certain subject matter and is not to be regarded as an acquiescence in the merits of the rejection, including the Office's construction of the term "treating." Applicant reserves the right to prosecute claims to canceled subject matter in one or more continuing applications.

Claims 1-6, 11-13, 15, and 17-25 stand rejected under 35 U.S.C. § 102(e) as allegedly anticipated by Ferrara et al., U.S. 6,455,283. The Office believes that Ferrara teaches a polypeptide, VEGF-E, which has the exact amino acid sequence of SEQ ID NO:2, and thus comprises residues 230-345 of SEQ ID NO:2. The Office further believes that Ferrara teaches anti-VEGF-E antibodies and methods of treatment using the antibody and that Ferrara's antibodies "anticipate the antibodies to the polypeptide of SEQ ID NO:2 (as well as the claimed fragments)." The Office also believes that "producing antibodies to the full-length zvegf3/VEGF-E protein would necessarily result in antibodies that are specific for the claimed zvegf3 fragments and dimeric proteins of fragments" and that "Ferrara's method of treatment

using the antibody would inherently decrease zvegf3 activity in a mammal." The Office concludes that the reference anticipates claims 1-6, 11-13, 15, and 17-25.

This rejection is traversed in part and overcome in part. Independent claims 1, 11, and 17 have been amended to recite an antibody that specifically binds to a dimeric protein consisting of two polypeptide chains. The remaining claims include this limitation in view of their dependence on an amended claim. This amendment has been made solely to expedite prosecution of this application; the change from "having" to "consisting of" is not intended to alter the scope of the claims. The scope of "having" is interpreted in light of the specification (MPEP 2111.03), which discloses that biologically active zvegf3 is, like other members of the PDGF family, a dimeric protein. The intended meaning of "having" is also clear from the context of the claims ("dimeric protein having two polypeptide chains, wherein each of said polypeptide chains consists of a sequence" [emphasis added]).

Applicant's amended claims recite an antibody that specifically binds to a dimeric protein consisting of two polypeptide chains, wherein each of said polypeptide chains consists of a sequence of amino acid residues selected from the group consisting of residues 230-345 of SEQ ID NO:2, residues 231-345 of SEQ ID NO:2, residues 232-345 of SEQ ID NO:2, residues 233-345 of SEQ ID NO:2, residues 234-345 of SEQ ID NO:2, residues 235-345 of SEQ ID NO:2, residues 236-345 of SEQ ID NO:2, residues 237-345 of SEQ ID NO:2, residues 238-345 of SEQ ID NO:2, residues 239-345 of SEQ ID NO:2, and residues 240-345 of SEQ ID NO:2. The disclosure of Ferrara does not teach or suggest an antibody having the recited specificity, much less the claimed methods of reducing cell proliferation or extracellular matrix production caused by zvegf3 in a mammal, reducing fibrosis caused by zvegf3 in a mammal, or reducing stellate cell activation caused by zvegf3 in a mammal for the reasons discussed below. Ferrara does not teach or suggest the use, as an immunogen, of a protein as recited in Applicant's claims or a peptide fragment thereof. Ferrara teaches the use of "the VEGF-E polypeptide or a fusion protein thereof" as an immunogen. See, column 54, lines 27-28 and 52-53. When these statements are read in light of the disclosure at column 7, lines 61-67 (defining "VEGF-E polypeptide") and column 8, lines 15-29 (defining "VEGF-E variant"), one is taught to use as an immunogen a native VEGF-E sequence or "an active VEGF-E polypeptide . . . having at least about 80% amino acid sequence identity with the VEGF-E polypeptide having the deduced amino acid sequence shown in FIG.2 for a full-length native sequence VEGF-E polypeptide." For the reasons discussed below, the use of such an immunogen would not be expected to produce an antibody as recited in Applicant's claims. Thus, Ferrara fails to teach, either explicitly or inherently, Applicant's claimed invention.

Enclosed herewith is a Declaration of Christopher Clegg Under 37 C.F.R. § 1.132. As stated by Dr. Clegg, it is likely that the zvegf3 growth factor domain (residues 235-345 of SEQ ID NO:2) is buried within the full-length, precursor form of the protein and becomes exposed only after cleavage between the interdomain region and the growth factor domain. Dr. Clegg thus concludes that if an animal were immunized with a polypeptide comprising at least about 80% of the VEGF-E sequence disclosed by Ferrara et al., one skilled in the art would not reasonably expect to obtain an antibody that specifically binds to a protein consisting of two polypeptide chains as recited in Applicant's claims.

The role of the amino-terminal CUB domain in sterically inhibiting the activity of the growth factor domain of PDGF-C (Applicant's zvegf3; Ferrara's VEGF-E) is now recognized in the art. Li et al. (*Nature Cell Biol.* 2:302-309, 2000; of record) teach that the conformation of full-length PDGF-C blocks the active region of the molecule:

> Instead the CUB domains are thought to sterically block the receptor-binding epitopes in the unprocessed dimer. This idea is supported by two lines of evidence, from studies of the PDGF-CC core domain and of plasmin-treated full-length PDGF-CC. [Page 307, right column.]

A similar analysis of PDGF-C structure and function is disclosed by Fredriksson et al. (*Cytokine and Growth Factor Reviews* 15:197-204, 2004; copy enclosed) at page 198, right column:

> Thus, one important role of the CUB domains in the novel PDGFs is to prevent the full-length proteins to bind their cognate receptors by sterically blocking the receptor binding surfaces of the growth factor domains, until extracellular proteases have removed the CUB domains.

The publication of Fredriksson et al. is cited to show a fact, i.e., the characteristics and properties of PDGF-C. In view of the structure of zvegf3 (PDGF-C or VEGF-E), including the role of the CUB domain in sterically blocking epitopes in the growth factor domain, there is no reasonable expectation that immunization according to the teachings of Ferrara et al. would result in the antibodies recited in Applicant's claims.

Antibodies raised against full-length zvegf3 at ZymoGenetics, Inc., the assignee of the instant application, did not bind to zvegf3 growth factor domain. These experiments are described in the enclosed Declaration of Henry Francis Pelto III Under 37 C.F.R. § 1.132. As described in that declaration, Mr. Pelto tested the binding specificity of rabbit polyclonal antisera that was raised against a full-length human zvegf3 protein fused to maltose binding protein. The antisera bound to fused and unfused full-length human zvegf3, but did not bind to isolated

human zvegf3 growth factor domain (i.e., residues 235-345 of SEQ ID NO:2), when tested in a Western blot format.

In summary, the art of record, in combination with the experimental evidence discussed in Mr. Pelto's declaration, clearly establishes that (1) the receptor-binding epitopes in the growth factor domain of zvegf3 are sterically blocked by the amino-terminal portion of the full-length molecule and (2) immunogenic epitopes of the growth factor domain are similarly blocked. Thus, one of ordinary skill in the art would not reasonably expect that immunization with 80% or more of the full-length zvegf3 polypeptide would result in antibodies that specifically bind to an epitope within the growth factor domain.

In contrast to the disclosure of Ferrara, Applicant teaches the importance of the zvegf3 growth factor domain, including its biological activity (specification at pages 4-6, 38-39, and elsewhere). Applicant further teaches the use of peptides from within the growth factor domain as immunogens for raising anti-zvegf3 antibodies (specification at pages 33-34), as well as the use of purified zvegf3 growth factor domain as an immunogen for the generation of monoclonal antibodies (pages 34-36).

Applicant respectfully submits that the evidence discussed above, including the declaration of Mr. Pelto, unambiguously refutes the Office's assertions that "producing antibodies to the full-length zvegf3/VEGF-E protein would necessarily result in antibodies that are specific for the claimed zvegf3 fragments and dimeric proteins of such fragments" and that "the antibody of the prior art would necessarily bind to the dimeric protein of the present claims." Applicant's antibodies are thus neither explicitly taught nor inherently disclosed by Ferrara. Inherency must be certain. *Ex parte Cyba*, 155 USPQ 756, 757 (Bd. Pat. App. Int. 1966). See also, *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 220 USPQ 303, 314 (Fed. Cir. 1983) ("Anticipation of inventions set forth in product claims cannot be predicated on mere conjecture respecting the characteristics of products that might result from the practice of processes disclosed in references.") and *Trintec Indus., Inc. v. Top-U.S.A. Corp.*, 63 USPQ2d 1597, 1599 (Fed. Cir. 2002) ("Inherent anticipation requires that the missing descriptive material is 'necessarily present,' not merely probably or possibly present, in the prior art."). See also, *Toro Co. v. Deere & Co.*, 355 F.3d 1313 (Fed. Cir. 2004) ("For inherent anticipation, the '516 patent must have sufficiently described and enabled at least one embodiment that necessarily featured or resulted in the subject matter embraced by limitation (c)" [emphasis added]). In the present case, the art and experimental evidence show that both receptor-binding and immunogenic epitopes within the growth factor domain of zvegf3 are blocked by other sequences in the full-length molecule. Hence, immunization with 80% or more of full-length VEGF-E, or with a peptide

from a region other than the growth factor domain, would not be expected to produce the recited antibodies. Ferrara fails to direct one skilled in the art to use an immunogen that would be expected to elicit an antibody with the specificity recited in Applicant's claims. Thus, Ferrara does not teach or suggest the antibodies recited in Applicant's claims or the claimed methods of reducing cell proliferation or extracellular matrix production, fibrosis, or stellate cell activation. Reconsideration and withdrawal of the rejection under 35 U.S.C. § 102(e) are requested.

Applicants believe that each rejection has been addressed and overcome. Reconsideration of the application and its allowance are requested. If for any reason the Examiner feels that a telephone conference would expedite prosecution of the application, the Examiner is invited to telephone the undersigned at (206) 442-6673.

Respectfully Submitted,

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Enclosures:

Amendment Fee Transmittal (in duplicate)
1 Reference
Terminal Disclaimer (in duplicate)
Declaration of Christopher Clegg under 37 C.F.R. § 1.132
Declaration of Henry Francis Pelto III under 37 C.F.R. § 1.132
Postcard

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